The Rejection of Claims 60-70 Under 35 U.S.C. § 112, first paragraph

Claims 60-70 stand rejected under 35 U.S.C. § 112, first paragraph. The Final Office Action alleges that the specification does not provide a written description of the claimed invention. Applicants respectfully traverse this rejection and its supporting remarks.

The purpose of the written description requirement is to assure that the applicant was in possession of the claimed subject matter on the application filing date. *Vas-Cath Inc. v. Mahurkur*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1116-17 (Fed. Cir. 1991). It is well known that the specification need not describe subject matter of later-filed claims in *ipsis verbis* in order to satisfy the written description requirement. *In re Lukach*, 442 F.2d 967, 969, 160 U.S.P.Q. 795, 796 (C.C.P.A. 1971).

The Final Office Action states that "the sole reference to synthetic peptides occurs at the end of the summary of the invention." Importantly, **nothing** in the summary of the invention in the '501 specification in any way **limits** the application of the clear and unambiguous teaching: "Based on the nucleotide sequences, synthetic peptides may also be prepared." (page 3, lines 15-16).[1] "While some inventions require more disclosure, the adequacy of the description of an invention depends on its content in relation to the particular invention, not its length." *In re Hayes Microcomputer Products Inc. Patent Litigation*, 982 F.2d 1527, 1534, 25 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1992).

The Final Office Action further states that "[a]ssuming that applicant is correct and that

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[1] References to Applicants' specification are to pages and lines of the '501 specification unless noted otherwise.

one can remove the sentence from the context in which it occurs one still must have evidence from elsewhere in the specification to support ones [sic] position." (page 6, lines 12-14) There is no requirement in the law that the written description originate from any particular portion of the specification or that a description found in the summary of the invention must be supported elsewhere in the specification. On the contrary, the law requires that the specification be considered as a whole when determining whether it describes a particular invention. *In re Wright*, 9 U.S.P.Q. 1649, 1651 (Fed. Cir. 1989).

The particular invention at issue here is use of synthetic envelope polypeptides in an immunoassay. The '501 specification provides ample disclosure of envelope polypeptides. For example, the specification teaches that "polypeptides or immunologically active fragments thereof, may find use as diagnostic reagents, being used in labeled or unlabeled form . . . ." (page 11, lines 5-7) The specification further teaches that

> [t]he expression products of the env and gag genes and immunogenic fragments thereof having immunogenic sites may be used for screening antisera from patients' blood to determine whether antibodies are present which bind to hTLR antigens. A wide variety of assay techniques can be employed, involving labeled or unlabeled antigens. The label may be fluorescers, radionuclides, enzymes, chemiluminescers, magnetic particles, enzyme substrates, cofactors or inhibitors, ligands, or the like.
>
> A particularly convenient technique is to bind the antigen to a support and contact the blood sample with the antigen. After washing the support to remove non-specifically bound antisera, labeled antibodies to human Ig are added and specifically bound label determined.
>
> The antigenic polypeptide of hTLR may also be used as immunogens by themselves or joined to other antigens for the production of antisera or monoclonal antibodies which may be used for therapy or diagnosis. The immunoglobulins may be from any mammalian source, e.g., rodent, such as rat or mouse, primate, such as baboon, monkey or human, or the like. For diagnosis, the

> antibodies can be used in conventional ways to detect hTLR in a clinical sample.

(page 14, line 17 to page 15, line 4).

One of skill in the art who read the '501 specification at the time it was filed would readily perceive that the disclosure relating to use of expression products of the *env* gene was equally applicable to either recombinantly produced or synthetic envelope polypeptides, particularly in light of the teaching that "[b]ased on the nucleotide sequences, synthetic peptides may also be prepared." (page 3, lines 15-16; Young Declaration ¶ 9).[2]

The relevant question is whether the written description in the specification "convey[s] clearly to those skilled in the art, to whom it is addressed, **in any way**, the information that the applicant has invented the specific subject matter later claimed." *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976), *appeal after remand*, 646 F.2d 527, 209 U.S.P.Q. 554 (C.C.P.A. 1981) (emphasis added). Applicants' '501 specification conveys this information by disclosing the coding sequence of the *env* gene (Figure 4), teaching how polypeptide products of the *env* gene can be used in immunoassays (page 11, lines 3-9; page 14, lines 17-32), and pointing out that synthetic peptides can also be prepared (page 3, lines 15-16). Under controlling precedent, this disclosure in the '501 specification is more than adequate to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request withdrawal of this rejection of claims 60-70. If the Examiner maintains this rejection, Applicants request under 37 C.F.R. §1.104(d)(2) that the Examiner provide an affidavit setting forth the factual basis for the rejection.

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[2] References to the Young Declaration are to the Young Declaration of March 19, 1997 unless noted otherwise.

The Rejection of Claims 60-70 Under 35 U.S.C. § 112, first paragraph

Claims 60-70 stand rejected under 35 U.S.C. § 112, first paragraph. The Final Office Action continues to assert that Applicants' specification does not provide "necessary guidance as to which peptide to make so that there would be a reasonable expectation that it would function in the assay methods presented in applicant's specification." (page 4, lines 7-10). Applicants respectfully traverse this rejection and its supporting remarks.

The Patent Office has asserted that undue experimentation would be required to practice Applicants' claimed invention. The Patent Office has asserted that the envelope protein's amino acid sequence alone is insufficient to enable one of skill in the art to make synthetic peptides for use in immunoassays (Paper No. 28 at page 7, lines 16-17), has applied the factors discussed in *Ex parte Forman*, 230 U.S.P.Q. 546 (Bd. Pat. App. Interf. 1986) to the subject application, and has concluded that the specification is not enabling. (Paper No. 28 at page 10, line 23 to page 14, line 3). Applicants disagree with the conclusion and address each of the *Forman* factors as follows.

Quantity of experimentation necessary. The Patent Office states that there is "**no way** to predict how much experimentation is required to obtain a synthetic peptide which will permit the detection of anti-*env* [sic] antibodies in patient sera." (Paper No. 28 at page 12, lines 24-26) (emphasis added). This assertion is simply not accurate. The very fact that amino acid sequences of the envelope protein identified by the Hopp algorithm as the most likely immunogenic regions of the protein are recognized by antisera from AIDS patients demonstrates that it would not require much experimentation at all for one to generate synthetic envelope peptides which would

be recognized by antibodies in patient sera. (Young Declaration ¶11).

The amount of direction or guidance presented. The Patent Office asserts that the specification does not provide guidance with respect to use of synthetic peptides in immunoassays. (Paper No. 28 at page 13, lines 27-28). As demonstrated above, however, the '501 specification does provide ample teachings regarding the use of peptides in immunoassays. (Young Declaration ¶¶ 9 and 16). Also as pointed out above, one of skill in the art would recognize that both synthetic peptides and recombinant peptides could be used in these assays. (Young Declaration ¶ 9). The Patent Office itself recognizes that antibodies cannot tell the difference between a peptide which is recombinantly produced and one which is produced synthetically: "it is unclear that an antibody which recognizes a particular epitope makes any such clear distinction [between a synthetic peptide and a peptide fragment generated by some other means]." (Paper No. 28 at page 3, lines 13-14).

The presence or absence of working examples. Under controlling precedent, the Patent Office cannot require working examples in order to enable the invention. *In re Long*, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). To the contrary, whether the specification does or does not contain working examples is only one factor to be considered in determining enablement. *In re Honn*, 150 U.S.P.Q. 652, 657 (C.C.P.A. 1966). The relative skill of those in the relevant art must also be considered. *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. Interf. 1986). Based on the level of skill in the art, the lack of working examples is not determinative of non-enablement, because there is ample demonstration in the relevant art that ordinary artisans can practice immunoassays using synthetic peptides and can determine which regions of any given protein are likely to be immunogenic. (Young Declaration ¶¶ 10-16). The art demonstrates

clearly that at the time of the invention those skilled in the field of immunoassays would have been able to determine which regions of the envelope protein were likely to be immunogenic and to use these regions in standard immunoassays. *Id.* Applicants can properly rely on common knowledge in the art to bolster and supplement its disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

The nature of the invention. Applicants agree with the Examiner's characterization of the nature of the invention as synthetic peptides from the *env* gene of HIV (a gene whose sequence is set forth) and the use of these peptides in immunoassays. (Paper No. 28 at page 10, lines 20-22).

The state of the prior art. Applicants agree that the art was uncertain as to the location and identity of the HIV *env* gene and protein. The Patent Office dismisses Applicants' contribution to this art by alleging that "the presence of an open reading frame in and of itself does not mean that the actual proteins encoded thereby [have] been demonstrated." (Paper No. 28 at page 12, lines 17-19). However, it is Applicants' description of the coding sequence of the *env* gene and other HIV genes which taught the correct location and identity of the *env* gene, and the amino acid sequence which the *env* gene encodes. Sanchez-Pescador *et al.*, SCIENCE 227, 484-92 (February 1, 1985). This was a valuable and stabilizing contribution to an art which was "in flux" and which was avidly seeking diagnostic and therapeutic solutions to the HIV epidemic.

The relative skill of those in the art. Applicants agree with the Examiner's statement that the level of skill in the art was high. (Paper No. 28 at page 11, lines 13-15).

The predictability or unpredictability of the art. The art which the Patent Office argues is unpredictable is too narrowly defined. In the Office Action mailed May 28, 1997, the Patent Office asserts that immunoassays employing synthetic peptides of the HIV envelope protein were

not known at the time the '501 application was filed. (Paper No. 28 at page 11, lines 9-11). Applicants respectfully point out that the novelty of their invention lies in the use of synthetic HIV envelope peptides in immunoassays; therefore, one would not expect assays employing these peptides to be known at the time Applicants' first application was filed. The relevant art is the use of synthetic peptides in immunoassays. Use of synthetic peptides in immunoassays **was known and widely practiced** at the time the '501 specification was filed. (Young Declaration of ¶ 8).

The breadth of the claims. The Patent Office has stated that the actual number of peptide species is not *a priori* determinable. (Paper No. 28 at page 10, lines 26-27). However, Applicants need not exemplify every species encompassed within the claims. *In re Cavallito and Gray*, 127 U.S.P.Q. 206 (C.C.P.A. 1960), requires that "the selection of the examples and other exemplary material used as the disclosure to support a claim must be adequately representative of the area covered by it." 127 U.S.P.Q. at 209. Appellants have met this requirement by providing the nucleotide coding sequence for the *env* gene, which permits the amino acid sequence of the envelope protein to be known and available for use in constructing synthetic peptides. As the Court of Customs and Patent Appeals stated in *In re Grimme*, 124 U.S.P.Q. 499 (C.C.P.A. 1960), "[i]t is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." 124 U.S.P.Q. at 502.

Specific teachings in Applicants' specification, together with general knowledge in the art at the time the subject application was filed, provide those of skill in the art with the requisite detail necessary to make and use Applicants' claimed invention. (Young Declaration ¶19.) As

stated in *In re Surrey*, 151 U.S.P.Q. 724 (C.C.P.A. 1966), "it would appear to serve no useful purpose to lengthen the disclosure further with examples of compounds which 'can be prepared' . . . ." 151 U.S.P.Q. at 728.

Thus, in contrast to the conclusions reached by the Patent Office, application of the *Forman* factors to Applicants' '501 specification clearly demonstrate that the specification enables the full scope of the invention claimed.

The Final Office Action has also cited *Genentech Inc. v. Novo Nordisk A/S*, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997), as supporting its position that the subject invention is not enabled across its full scope. The Final Office Action misapplies *Genentech* to Applicants' specification; the technology of the subject application is easily distinguishable from that involved in *Genentech*. In that case, Genentech sought claims to a method of producing human growth hormone using cleavable fusion. 42 U.S.P.Q.2d at 1002. The court found that, at the time Genentech filed its parent application, the art regarded cleavable fusion as "an unpredictable technology in the early stages of development . . . ." *Id.* at 1006. Thus, the court found that Genentech's specification provided insufficient detail to permit one of skill in the art to practice the claimed invention. *Id.*

However, the technology involved in the subject application, *i.e.*, immunoassays using synthetic polypeptides, was neither unpredictable nor in an early stage of development when the '501 specification was filed. The relevant technology is the use of synthetically prepared polypeptides in immunoassays. The ability to prepare polypeptides synthetically was well known at the time the subject application was filed, as were numerous types of immunoassays. (Young Declaration ¶7). In fact, the predictability of the art was so advanced that skilled artisans were

able to create a model, the Hopp and Woods hydrophilicity plotting method (the "Hopp algorithm"), with which to predict antigenic sites on proteins. T.P. Hopp *et al.*, PROC. NATL. ACAD. SCI. USA 78, 3824 (June 1981); T.P. Hopp and K.R. Woods, MOL. IMMUNOL. 20, 483 (1983). The Hopp model has been shown to predict accurately which determinants on a particular protein are antigenic. T.P. Hopp, PEPTIDE RESEARCH 6, 183 (1993); (Young Declaration ¶¶ 11 and 12). One cannot construct a workable model without sufficient understanding of the parameters involved. Thus, when Applicants filed the '501 application the technology of employing synthetic peptides in immunoassays was at an advanced stage in the art and, unlike cleavable fusion at the time Genentech's application was filed, was far from unpredictable.

The court in *Genentech* also stated that the specification "must supply the novel aspects of an invention in order to constitute adequate enablement." 42 U.S.P.Q.2d at 1005. The novel aspect of Applicants' claimed invention lies not in the use of polypeptides in immunoassays, or even the use of synthetic polypeptides in immunoassays, but in the use of **synthetic HIV envelope polypeptides** in immunoassays. Applicants have supplied key starting material for practicing the invention, which is the nucleotide coding sequence of the ARV-2 *env* gene and the amino acid sequence it encodes. Both the nucleotide sequence and the amino acid sequence were correct, which permits the amino acid sequence of the envelope protein to be known and used. (*See* Sanchez-Pescador *et al.*, 1985). As stated in *Genentech*, "the omission of minor details does not cause a specification to fail to meet the enablement requirement." *Id.* One of skill in the art would have understood that polypeptides which are produced synthetically can be used in immunoassays described in the '501 specification. (Young Declaration ¶ 9). The specification

itself states that synthetic peptides may be prepared. (page 3, lines 15-16). This is the type of minor detail which the *Genentech* court confirmed need not be disclosed in the specification. 42 U.S.P.Q.2d at 1005, citing *Hybritech*, 802 F.2d at 1385, 231 U.S.P.Q. at 94. Indeed, as the Office Action mailed May 28, 1997 itself points out, "it is unclear that an antibody which recognizes a particular epitope makes any such clear distinction [between a synthetic peptide and a peptide fragment generated by some other means]." (Paper No. 28 at page 3, lines 13-14).

Both the Office Action mailed May 28, 1997 and the Final Office Action found the art cited in the Young Declaration of March 19, 1997 deficient because that art did not use the Hopp algorithm. The discussion in the Young Declaration of the cited art in relation to the Hopp algorithm has been misunderstood. The fact that the studies cited in the Young Declaration did not employ the Hopp algorithm is irrelevant to the point which the Declaration makes: the Hopp algorithm identifies epitopes which are antigenic. For example, Young points out that the Hopp algorithm predicts that the most hydrophilic region of the ARV-2 envelope protein is residues 738-743 (ERDRDR), the next most hydrophilic region is residues 653-58 (EKNEQE), and the third most hydrophilic region is residues 733-738 (EEEGGE). (Young Declaration ¶ 11). Young then points out that actual tests employing sera from AIDS patients identify synthetic peptides containing these same amino acid sequences. *Id.* The strength of this demonstration is that the Hopp algorithm **does** predict antigenic regions of the ARV-2 envelope protein which, if present in synthetic polypeptides, can be identified by antibodies in the sera of AIDS patients.

The '501 specification, together with the knowledge and skill in the art at the time the application was filed, clearly enables the full scope of the present invention. Furthermore, in litigation between Chiron and Abbott Laboratories involving Luciw U.S. Patent 5,156,949,

Abbott vigorously asserted that the October 31, 1984 parent application did not enable an immunoassay employing recombinant envelope antigens. The court considered Abbott's arguments and evidence, then ruled against Abbott. The court stated, "given the declarations of the parties' experts as to the guidance provided by the patent, the presence of working examples, the state of the prior art, and the relative skill of those in the art, this court cannot conclude by clear and convincing evidence that the '949 Patent does not enable one skilled in the art to practice the invention **with any HIV strain**." (See Amended Memorandum and Order re Defense of Enablement, 1996 U.S. Dist. LEXIS 4802, submitted as part of the IDS; emphasis added).

The '501 specification has thus been judged enabling for the practice of immunoassays employing recombinant env antigens **of any HIV strain**. Logic dictates that the '501 specification also enables the practice of immunoassays employing synthetic env antigens of any HIV strain, as attested by Dr. Young. (Young Declaration B ¶ 9).

Applicants respectfully request withdrawal of this rejection of claims 60-70. If the Examiner nevertheless maintains this rejection, Applicants request under 37 C.F.R. § 1.104(d)(2) that the Examiner provide an affidavit setting forth the factual basis for the rejection.

The Rejection of Claims 60-70 Under 35 U.S.C. §§ 102(b) and 102(e)

Claims 60-70 stand rejected under 35 U.S.C. §§ 102(b) and 102(e) as being anticipated by Chang *et al.*, U.S. Patent 4,7714,175, and Cosand, U.S. Patent 4,629,783. Applicants respectfully traverse this rejection and its supporting remarks.

As established above, the present invention is fully described and enabled by its parent '501 specification and therefore has a priority date of October 31, 1984. Both Chang *et al.* and Cosand were filed after the '501 application. Therefore, neither reference qualifies as prior art.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 60-70 Under 35 U.S.C. § 103(a)

Claims 60-70 stand rejected under 35 U.S.C. § 103(a) as being obvious over either the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.*, or in combination with Levy, U.S. Patent 4,716,102 and in view of the level of skill in the art as set forth in the Young Declaration of March 19, 1997. Applicants respectfully traverse this rejection and its supporting remarks.

Applicants' invention requires knowledge of the amino acid sequence of the AIDS virus envelope protein, because Applicants' claims recite a **synthetic** polypeptide. One cannot synthesize a polypeptide without knowing its amino acid sequence. The Patent Office has the burden of establishing a *prima facie* case that Applicants' invention, including the amino acid sequence of the envelope protein, is obvious. *See, e.g., In re* Rijckaert, 29 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993) ("In rejecting claims under 35 U.S.C. 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness . . . ."). Applicants' invention is not obvious over the combined teachings cited in the Final Office Action because (1) none of these teachings disclose the amino acid sequences of an immunogenic envelope protein of an unambiguously identified AIDS virus and (2) none of these teachings disclose means by which such proteins could be obtained in sufficient quantity to determine its amino acid sequence. Therefore, the Final Office Action has failed to establish a *prima facie* case of obviousness based on the combined teachings.

Applicants have pointed out the confusion which existed in the art in 1984, at the time the '501 application was filed. In response, the Final Office Action states that Applicants have not set

forth exactly what in the art was confusing.

What was confusing in the art at the time the '501 application was filed was nothing less than the **very identity** of the virus which caused AIDS. This confusion is clearly evidenced by the fact that two of the most active and well-respected AIDS research laboratories in the world, the laboratories of Luc Montagnier and Robert C. Gallo, did not agree even on the family to which the "AIDS virus" belonged, much less agree on its actual identity. Montagnier's group postulated that the virus was related to equine infectious anemia virus (EIAV). Montagnier *et al.*, SCIENCE 225, 63-66 (1984). Gallo's group, on the other hand, announced that the virus was "a true member of the HTLV family," Schupbach *et al.*, SCIENCE 224, 503-505 (1984), an identification which was later found to be erroneous. Gallo, VIRUS HUNTING: AIDS, CANCER, AND THE HUMAN RETROVIRUS: A STORY OF SCIENTIFIC DISCOVERY, at pages 143 and 152 (New Republic Books, 1991); Young Declaration ¶ 19. Identification of the AIDS virus was an important issue in 1984, and one of ordinary skill in the art would certainly have read these two publications from eminent scientists in the field. It is equally clear that one of ordinary skill in the art, reading these two publications, would not have been confident that the identity of the virus which caused AIDS had been established.

Popovic *et al.* provides further evidence of the confusion and uncertainty surrounding identification of the AIDS virus:

> The transient expression of cytopathic variants of HTLV in cells from AIDS patients and the previous lack of a cell system that could maintain growth and still be susceptible to and permissive for the virus represented a major obstacle in detection, isolation, and elucidation of the precise causative agent of AIDS.

Popovic *et al.*, Science 224, 497, 500 (1984). The difficulty of growing the AIDS-causing virus

in vitro was well known in 1984. (Young Declaration ¶ 17).

The art cited by the Patent Office reflects this confusion. For example, there is no indication in Schupbach *et al.* that envelope proteins had been identified by antibodies in the sera of the AIDS patients which were tested. The authors of Schupbach *et al.* themselves characterized their report as a "**preliminary** biochemical and immunological analysis." SCIENCE 224 at 503 (emphasis added). The report provides no amino acid sequence data. The only mention of envelope proteins in the entire article is at page 505, at the top of column 2, which states:

> The detection of p65 by many of the serum samples is of special interest. We have tested these sera on strips prepared from lysates of cells producing HTLV-I or -II. Some of the cells produce a p65 that has been shown (*13*) to be coded for by the *env* gene of HTLV-I and to be the homolog of the gp61 described by others (*11, 12*). Many of the sera recognizing p65 in HTLV-III-infected cells also recognized, **though somewhat faintly**, p65 in cells producing HTLV-I or -II, and some of them also recognized *gag*-related antigens (data not shown).

Id. at 505 (emphasis added). The reference which is cited as teaching that the *env* gene of HTLV-I encodes a 65 kD protein (reference 13) is a manuscript of Schupbach, Sarngadharan, and Gallo, which at the time of the publication of Schupbach *et al.* was **in press** and therefore not available to those of skill in the art. (*See* reference list of Schupbach *et al.* at page 505). It is axiomatic that those of ordinary skill in the art do not accept conclusions of a scientific report until the data which underlies those conclusions has been examined and, preferably, replicated. The cited passage goes on to point out that the recognition of p65 by sera of AIDS patients was "faint." A faint immune response would not lead one of ordinary skill in the art to the conclusion that the p65 protein, whatever its identity, would be a good candidate for use in diagnostic immunoassays.

In fact, even the authors of Schupbach *et al.* do not assert that they had truly identified **viral** protein antigens. Schupbach *et al.* characterized the immunoreactive proteins they detected as "**either** virus-coded proteins **or** cellular antigens specifically induced by the infection." *Id.* at page 505 (emphasis added). Therefore, Schupbach *et al.* not only does not teach the amino acid sequence of an envelope protein, it does not even unambiguously identify an envelope protein.

Sarngadharan *et al.* separated protein components from purified HTLV-III using SDS-polyacrylamide electrophoresis; among these protein components was "a protein with a molecular weight of 41,000 (**presumably** the envelope glycoprotein) . . . ." SCIENCE 224, 506, 507 (May 4, 1984), emphasis added. Again, at page 508, Sarngadharan *et al.* refers to the 41 kD immunoreactive protein as being "**presumably** the envelope protein." As in Schupbach *et al.*, no amino acid sequence data is provided. Furthermore, the immunoreactive protein identified in Sarngadharan *et al.* has a molecular weight of 41 kD, compared with the 65 kD protein identified in Schupbach *et al.* It would certainly not be clear to the artisan of ordinary skill how a 41 kD and a 65 kD protein could both be the envelope protein of the AIDS virus. One would at least be led to reserve judgment about which, if indeed either, of the 41 or 65 kD proteins might be the envelope protein.

Similarly, Popovic *et al.* barely mention envelope proteins in their 1984 report:

> Also consistent with an HTLV etiology were the results of Essex and Lee and their colleagues showing the presence of antibodies to cell membrane antigens of HTLV-infected cells in serum samples from more than 40 percent of patients with AIDS (*23*). This antigen has since been defined as part of the envelope of HTLV (*24*).

SCIENCE 224, 497, 497 (May 4, 1984). Again, the cited references were **in press** and thus were unavailable to those of skill in the art. *See* reference list at page 500. Popovic *et al.* does not

even provide a molecular weight for the alleged envelope protein antigen.

Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* cite references which are not publicly available, do not disclose amino acid sequence data, and disagree even on a possible molecular weight for an envelope protein antigen. Thus, the meager combined teachings in Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* regarding envelope protein antigens could not lead one of ordinary skill in the art to Applicants' invention, which requires knowledge of the amino acid sequence of the AIDS virus envelope protein.

Teachings in the cited references regarding the cell line which could be used to propagate the HTLV-III virus are similarly defective. Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* all originated from Gallo's laboratory and all employed the same cell line. Sarngadharan *et al.* discloses only that "virus was purified from supernatants of cell cultures supporting the continuous production of HTLV-III" and refers to Popovic *et al.* SCIENCE 224 at 507. Schupbach *et al.* states only that "two immortalized and infected human T-cell clones, H4/HTLV-III and H17/HTLV-III" were used and also refers to Popovic *et al.* SCIENCE 224 at 503.

Popovic *et al.* states only that the cell line is a "neoplastic aneuploid T-cell line, derived from an adult with lymphoid leukemia . . . ." SCIENCE 224 at 498. The cell line itself is not described in detail. No culture conditions, beyond the use of RPMI 1640 medium containing fetal calf serum, antibiotics, and T-cell growth factor (IL-2) are provided. This is a very generic set of media components. It was well known in the art in 1984 that the growth requirements of mammalian cells are complex and determination of optimal growth media can be problematic. R.G. Ham, in *Tissue Growth Factors*, HANDBOOK OF EXPERIMENTAL PHARMACOLOGY, Vol. 57, page 13 (R. Baserga, ed.), 1981; H.R. Maurer, *Towards chemically-defined, serum-free media*

for mammalian cell culture, in ANIMAL CELL CULTURE, A PRACTICAL APPROACH, pp. 13-31 (R.I. Freshney, ed.), 1984. Given the well-known difficulty of maintaining AIDS virus-infected cells *in vitro*, one of skill in the art would not have had a reasonable expectation that establishing a neoplastic aneuploid T-cell line from an adult with lymphoid leukemia, without guidance as to the characteristics of the cell line or even how to maintain it in culture, would be successful. (Young Declaration ¶ 17).) In fact, a more reasonable conclusion from reading Popovic *et al.*, together with a background knowledge of the state of the art, would have been that the cells from this particular patient were unique and that there were tricks, not revealed in Popovic *et al.*, which permitted growth of retrovirus-infected cells *in vitro*. As the patient is identified in the report only by initials, there would have been no reasonable or ethical way for an ordinary artisan to have obtained another sample of these cells and to have established another useful cell line.

Furthermore, it was not certain in 1984 that Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* were indeed working with **the** AIDS virus. In 1984, at the time Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* were published, the state of the art did not permit the conclusion that HTLV-III was the causative agent of AIDS. Therefore, even if the references disclosed amino acid sequences and/or sufficient information to reproduce the cell line, they would not make Applicants' invention obvious because one could not have been certain that the relevant virus had been identified conclusively.

Even if, *arguendo*, one were to assume that in 1984 the identification of the AIDS virus had been established conclusively, the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* could not have led an ordinary artisan to Applicants' claimed invention. None of these references conclusively identify **any** protein as an envelope protein. None of these

references provide amino acid sequences. None of these references provide details for obtaining or propagating the cell line used in order to obtain quantities of the viral proteins or genes for sequencing. Thus, Applicants' invention, which requires knowledge of the amino acid sequence of the envelope protein of the causative agent of AIDS, cannot be obvious in view of the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.*, and the combined teachings of the cited references do not establish a *prima facie* case of obviousness.

Neither Levy U.S. Patent 4,716,102 nor the level of skill in the art described in the Young Declaration of March 19, 1997 can cure the deficiencies of the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* Levy discloses an AIDS-associated retrovirus, ARV-2, and a human T cell line infected with ARV-2. Nowhere does Levy teach or suggest that ARV-2 is the HTLV-III virus of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* As the '501 specification points out, this relationship could only be determined by sequencing the genomes of the two viruses and demonstrating that they are identical. (page 1, lines 26-32). Again, the Final Office Action uses impermissible hindsight to make this connection.

Nor can the state of the art, as described in the Young Declaration of March 19, 1997, fill in the gap which is missing from Schupbach *et al.*, Sarngadharan *et al.*, Popovic *et al.*, and Levy. Applicants' invention requires knowledge of the amino acid sequence of the AIDS virus envelope protein. No amount of skill in the art can render use of synthetic polypeptides in an immunoassay obvious if the starting material from which the amino acid sequence can be obtained is not sufficiently described or taught.[3]

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[3] Furthermore, because of the mutable nature of HIV viruses, the cell cultures infected with HIV virus, such as the cells used in the cited references, will comprise *env* sequences which vary slightly. (Young Declaration B ¶ 16). It would not have been obvious that an immunoassay

None of the cited references provide sufficient disclosure of a starting material which would provide one of ordinary skill in the art with a reasonable expectation of success of identifying immunogenic envelope polypeptides of a virus which causes AIDS. It is Applicants who first disclosed the complete sequence of an HIV isolate and the first accurate identification of the *env* gene and its reading frame. It is Applicants' description of the *env* gene and reading frame which permits synthetic production of env polypeptides with defined amino acid sequences for diagnostic and therapeutic purposes. The amino acid sequence of the envelope protein is not obvious from any combinations of teachings cited in the Final Office Action. It is impermissible to use hindsight to select these references and to assert that, because it is now known that the virus studied in the cited references and whose sequence is taught in Applicants' specification was in fact the HIV virus, that the references would have led one of ordinary skill to determine the amino acid sequence of that virus' envelope protein, synthesize envelope polypeptides, and use the synthetic polypeptides in immunoassays at the time the '501 application was filed.

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

In re Rouffet, Fed. Cir. No. 97-1492 (July 15, 1998).

Neither the Office Action mailed May 28, 1997 nor the Final Office Action provides any motivation for one of ordinary skill, working in a confused field, to combine references which

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employing synthetic or recombinant polypeptides would work in view of the known heterogeneity of the virus.

themselves contributed to that confusion. Therefore, the Final Office Action has failed to carry its burden of establishing a *prima facie* case of obviousness. The rejection must therefore be overturned. *In re Rijackaert*, 28 U.S.P.Q.2d at 1956 ("If the examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned."). Applicants respectfully request withdrawal of this rejection of claims 60-70.

The Rejection of Claim 68 Under 35 U.S.C. § 112, first paragraph

Claim 68 stands rejected under 35 U.S.C. § 112, first paragraph. The Final Office Action states that the specification does not provide support for peptides having at least 15 amino acids from the *env* region. Applicants respectfully traverse this rejection.

The '501 specification states that DNA sequences "encoding an amino acid sequence capable of specific binding to a receptor, e.g., an immunoglobulin, will be 27 bp, usually at least 45 bp, exclusive of the initiation codon." (page 9, lines 7-12). The DNA sequence of at least 45 bp encodes a polypeptide of at least 15 amino acids.

Applicants respectfully request withdrawal of this rejection.

Summary

The present invention is described in the '501 specification because that specification describes use of recombinantly produced envelope polypeptides in immunoassays and teaches that synthetic envelope peptides can be prepared. The skilled artisan would have understood that synthetic envelope peptides could be used in the immunoassays described in the '501 specification (Young Declaration ¶ 9).

The present invention is enabled in the '501 specification because it provides a starting material, which is the coding sequence of the *env* gene, teaches how to use envelope peptides in

immunoassays, and points out that synthetic peptides can be prepared. The relevant art at the time the '501 application was filed was fully capable of determining immunogenic regions of a protein, constructing synthetic peptides comprising these regions, and using such peptides in immunoassays. (Young Declaration ¶¶ 10-16).

Because the '501 specification describes and enables the claimed invention, the invention is not anticipated by either Chang *et al.* or Cosand.

The combined teachings cited in the Final Office Action do not render the invention *prima facie* obvious because they disclose neither an amino acid sequence of an AIDS virus envelope protein nor a readily available starting material from which to isolate and sequence an unambiguously identified AIDS virus envelope protein.

In view of the arguments stated above, Applicants respectfully request withdrawal of all the rejections and a speedy allowance of all pending claims. Please continue to address all further correspondence in this application to Alisa A. Harbin, Registration No. 33,895, Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

Dated: August 17, 1998 By: Vijay Pathak Reg. No. 38,266 for 8/17/98

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